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Effect of natural uranium on bone cells

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Natural uranium (NU), a mix at equilibrium of U-238, U-235 and U-234, is a natural element of the earth crust presenting a dual toxicity related both to its radiological effects as an alpha emitter and its chemical effects due to its metals properties. In atmospheric conditions and in most environmental systems, uranium is found in its oxocationic form $\{U(VI)O^{2+}_2\}$ that is the most stable form of uranium at formal oxidation state +VI simply referred as "U(VI)" hereafter.

Although many studies have investigated the effects of acute U(VI) exposure on living organisms, the consequences of chronic exposure to low doses on various cell fonctions remain elusive. The large majority of ingested U(VI) is rapidly excreted, however once it reaches the blood compartment, close to 20% will end up in skeletal tissue considered as the long term storage organ.

Considering the low specific activity of NU, we have adressed the chemical toxicity of this actinide on the viability, and function of the bone cells in charge of bone turnover: osteoblasts (OB), the cells in charge of bone matrix synthesis and mineralisation, osteoclasts (OC), the ones taking care of bone degradation and resorption, and osteocytes (OST), the more abundant ones, acting as mechanosensors and orchestrators of bone remodeling .

Using a rodent osteoblastic cell line (UMR-106), we have shown that the presence of U(VI) at sub-toxic concentrations as low as 25 µM, alters the matrix mineralization function. In comparison, investigating the effect of U(VI) of a mouse osteocyte cell line (MLO-A5), we observed that although the cytotoxicity index was more than twice higher than for the OB cell line, the mineralization function of these cells was affected starting at 2.5 µM of U(VI). Moreover, when exposed to sub-toxic doses of U(VI) for 24hrs, we could observe in both models the presence of needle like structures outside the cells as well as within vesicles inside the cells by Transmission Electron Microscopy. In order to determine the speciation of uranium in these models, EXAFS spectroscopic analysis was undertaken and revealed the presence of autunite forms of this actinide in both OB and OST cell types.

The involvment of autophagy, a self cleaning and recycling process, also shown to be crucial for mineralization of OB, has been investigated upon U(VI) exposure in OB and OST and will be discussed.

Finally, we examined the consequences of U(VI) exposure on both a pre-osteoclastic cell line (RAW264.7) as well as primary murine osteoclastic cells. We observed that when U(VI) is present in solution at concentrations in the µM range, it impairs OC formation,

mature OC survival, as well as mineral resorption function. We are presently investigating the effect of U(VI) imbedded in the matrix on the same processes.

Altogether, these results show that NU can affect the major bone cell types in their viability, differenciation and functions even at sub-toxic doses thereby impacting bone homeostasis.